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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/170,980	10/13/98	HILLMAN J	PF-0195-1DIV

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INCYTE PHARMACEUTICALS INC
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EXAMINER	
DAVIS,M	
ART UNIT	**PAPER NUMBER**
1642	18

DATE MAILED: 01/09/01

Please find below and/or attached an Office communication concerning this application or pr ceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/170,980	Hillman et al
Examiner	**Group Art Unit**
Minh-Tam Davis	1642

☒ Responsive to communication(s) filed on *Jul 3, 2000*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1, 11-16, and 18-24* is/are pending in the application.

Of the above, claim(s) *11-16 and 21-24* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1 and 18-20* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 1, 18-20 are being examined.

The following are the remaining rejections.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH, NEW REJECTION

GK

Claims 1, 18-20 are indefinite, because the term "substantially" in claim 1 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

REJECTION UNDER 35 USC 101, NEW REJECTION

35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 1 and 18-20 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

The disclosed utilities for HPAK comprising the amino acid sequence of SEQ ID NO:1 or fragments thereof or a pharmaceutical composition comprising SEQ ID NO:1 include the prevention and treatment of diseases associated with expression of HPAK, such as cancer of the prostate, parotid gland and breast, production of and screening of agonists, antibodies and antagonists that specifically bind to HPAK. However, neither the specification nor any art of record teaches what HPAK is, what it does do. They do not teach a utility for any of the fragments or the derivatives claimed, do not teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases. The asserted utilities for HPAK, such as production of and screening of agonists, antibodies and antagonists apply to many unrelated polypeptide structures sequences. Therefore the asserted utilities are not considered "specific" utilities, i.e. they are not specific to HPAK. Additional disclosed utilities for HPAK include therapy and diagnosis of conditions and diseases characterized by expression of HPAK and for the production and characterization of antibodies and inhibitors of HPAK. The asserted utility of HPAK is based on the assertion that HPAK (SEQ ID NO:1) has chemical and structural homology to human pancreatic kallikrein , that in particular HPAK and human kallikrein share 54% identity and have rather similar hydrophobilicty plots, that HPAK has a 24 N terminal amino acid sequence which closely resemble signal sequence important for kallikrein secretion, that HPAK has three conserved amino acids critical for serine protease activity, amino acid D200 which is likely to confer chymotrypsinogen-like activity, and conserved 10 cysteines to form five disulfide bonds, and that it is expressed in cells from prostate, parotid gland and breast of cancer patients. However, it is clear that, although there is a 54% identity between human pancreatic kallikrein and SEQ ID NO:1, there is a 46% dissimilarity between SEQ ID NO:1 and human pancreatic kallikrein, and

the effects of these dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, with 46% dissimilarity to human pancreatic kallikrein, the function of the SEQ ID NO:1 polypeptide could not be predicted, based on sequence similarity with human pancreatic kallikrein, nor would it be expected to be the same as that of human pancreatic kallikrein. In addition, Bork (Genome Research, 2000,10:398-400)

clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the errror rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrogngly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Clearly, given not only the teachings of Bowie et al, Lazar et al and Burgess et al but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, with a 46% dissimilarity to human pancreatic

kallikrein, the function of the SEQ ID NO:1 polypeptide could not be predicted, based on sequence similarity with human pancreatic kallikrein, nor would it be expected to be the same as that of human pancreatic kallikrein. Further, even if the polypeptide of SEQ ID NO:1 is a human pancreatic kallikrein-like protein, neither the specification nor any art of record teaches what the polypeptide is, what it does, does not teach a relationship to any specific disease or establish any involvement of the polypeptide in the etiology of any specific disease or teach which fragments might be active or which derivatives would function as claimed in a pharmaceutical composition. In addition, since SEQ ID NO:1 is only a predicted sequence, it is not even clear whether SEQ ID NO:1 does exist in nature. Further, even if SEQ ID NO:1 exists in nature, the specification does not disclose that SEQ ID NO:1 is produced at higher levels in cancer patients as compared to normal individuals, a critical feature that pancreatic kallikrein has for its use in diagnosis of prostate cancer. Moreover, the "specific" utility for SEQ ID NO:1 could not be asserted from its tissue specificity property, because the utility of SEQ ID NO:1 is shared by numerous other sequences, that are expressed and specific for the same tissue. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed nucleic acids. Because the claimed invention is not supported by a specific asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION, NEW REJECTION

Claims 1 and 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case

only sets forth SEQ ID NO:1 and therefore the written description is not commensurate in scope with the claims 11 and 20 drawn to naturally occurring sequences having at least 90% sequence identity with SEQ ID NO:1.

Claims 1 and 20 encompass an amino acid sequence encoded by an allelic sequence or variant of the DNA sequence encoding SEQ ID NO:1.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined. With the exception of SEQ ID NO:1, the skilled artisan cannot envision the detailed structure of the polypeptides encoded by the encompassed polynucleotides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The polypeptide encoded by the nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Although drawn specifically to the DNA art, the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly relevant to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Support for allelic sequences, i.e. variants, is provided in the specification on page 13, lines 11-18 where it is disclosed that the scope of the present invention includes alleles of the genes encoding HPAK, which may result from at least one mutation in the nucleic acid sequence. The specification further discloses that mutational changes are deletions, additions or substitution of nucleotides. However, no disclosure, beyond the mere mention of allelic variants is made in the specification. The claims and the specification encompass allelic sequences with any type of deletions, additions or substitution at any nucleotides, wherein the added or substituting nucleotide could be any nucleotide. This is insufficient to support the generic claims as provided by the Interim Written Description Guildlines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore only SEQ ID NO:1, but not the full breadth of the claims meets the written description provisin of 35 USC 112, first paragraph.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT, NEW

REJECTION

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

1. Claims 1, 18-20 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by a well established utility or a clear written description for the reasons set forth in the rejection under 35 USC 101 and 112, first paragraph above, one skilled in the art clearly would not know how to use the claimed invention.

2. Claims 19-20 are rejected under 35 U.S.C. 112, first paragraph.

Claims 19-20 are drawn to a pharmaceutical composition comprising SEQ ID NO:1 or fragments thereof, or a naturally occurring sequence having 90% sequence identity with SEQ ID NO:1.

Inherent in a pharmaceutical composition is the *in vivo* use thereof.

The specification contemplates the administration of HPAK, or antibodies or inhibitors of SEQ ID NO:1 or fragments thereof for treating cancer of the prostate, parotid gland or breast (p.23 and 28).

It is questionable that SEQ ID NO:1 could be used for treating cancer, because SEQ ID NO:1 is only a predicted sequence, and it is not clear whether SEQ ID NO:1 does exist in nature.

Further, even if SEQ ID NO:1 does exist in nature, one cannot extrapolate the teaching of the specification to the claims because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed SEQ ID NO:1 could be used for treating cancer. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of

neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed SEQ ID NO:1 could be used for treating cancer. In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2). In addition, anti-tumor agents and those that prevent, reduce, retard or eliminate secretion of metastatic promoters, must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the tumor or metastatic promotor producing cells and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. It is clear, as

disclosed above that the specification does not teach how to make/use a formulation with a targeting molecule. Also, the target cell must not have an alternate means of survival despite action at the proper site for the drug. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The formulation may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life of the formulation. In addition, the formulation may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the formulation has no effect, circulation into the target area may be insufficient to carry the formulation and a large enough local concentration may not be established. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success. The specification provides insufficient guidance with regard to the issues raised above and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE, NEW REJECTION

1. In the event that Applicant could overcome the above 101, and 112, first paragraph rejections, claims 1 and 20 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO:1, does not reasonably provide enablement for an amino acid sequence of SEQ ID NO:1, a biologically active fragment, or an antigencally active fragment of SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

Claims 1, 20 are drawn to an amino acid sequence of SEQ ID NO:1, or a biologically active fragment, or an antigenically active fragment of SEQ ID NO:1.

It is noted that a fragment could be as little as one amino acid, and an amino acid sequence could be as little as 2 amino acids. Although the specification discloses that HPAK (SEQ ID NO:1) has three conserved amino acids critical for serine protease activity, and amino acid D200 which is likely to confer chymotrypsinogen-like activity, there is no teaching of the actual biological activity of SEQ ID NO:1, nor characteristics of the claimed "biologically active fragment", or of an amino acid sequence of SEQ ID NO:1 which would distinguish the claimed "fragment" or "amino acid sequence" from any other fragments, or amino acid sequences of other sequences known in the art. Even if the

biological acitivity of the claimed polypeptide is serine protease-like or chymotrypsinogen-like activity, there is no teaching of the necessary size of the fragments that still retain the claimed biological activity, especially in view of the fact that only three conserved amino acids are proposed to be critical for serine protease activity, and one amino acid is proposed to be likely to confer chymotrypsinogen-like activity. Since detailed information regarding the structural, and functional requirements and properties of the claimed "biologically active fragment" or "amino acid sequence" of SEQ ID NO:1 are lacking, it would be undue experimentation for one of ordinary skill in the art to make and use the invention.

Further, there is insufficient guidance regarding the parameters and sequence of peptides, which correlate with their antigenic property, such as the ability to stimulate and generate CTLs. There is insufficient guidance regarding selection of peptides that meet the instant criteria of being antigenic, such as the ability to stimulate and generate CTLs. Since detailed information regarding the structural, and functional requirements and properties of the claimed "antigenically-active" are lacking, it would be undue experimentation for one of ordinary skill in the art to make and use the invention.

2. In the event that Applicant could overcome the above 101, and 112, first paragraph rejections, claims 1 and 20 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO:1, does not reasonably provide enablement for a naturally occurring sequence having 90% sequence

identity with of SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

Claims 1, 20 are drawn to a naturally occurring sequence having 90% sequence identity with of SEQ ID NO:1.

Claims 1 and 20 encompass an amino acid sequence encoded by an allelic sequence or variant of the DNA sequence encoding SEQ ID NO:1.

The specification discloses that the scope of the present invention includes alleles of the genes encoding HPAK, which may result from at least one mutation in the nucleic acid sequence (p.13, lines 11-18). The specification further discloses that mutational changes are deletions, additions or substitution of nucleotides. However, no disclosure, beyond the mere mention of allelic variants is made in the specification. The claims and the specification encompass polypeptides encoded by allelic sequences with any type of deletions, additions or substitution at any nucleotides, wherein the added or substituting nucleotide could be any nucleotide.

Applicants have not enabled proteins encoded by these types of modified polynucleotides in the specification.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin

binding, receptor binding and biological activity of the protein (Burgess et al. Journal of Cell Biology, 1990, 11: 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cell Biology, 1988, 8: 1247-1252). Similarly, it has been shown that aglycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies (see Tao. et al. The Journal of Immunology, 1989, 143(8): 2595-2601, and Gillies et al. Human Antibodies and Hybridomas, 1990, 1(1): 47-54). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

In view of the above unpredictability, one of skill in the art would be forced into undue experimentation in order to perform the claimed invention as broadly as claimed.

REJECTION UNDER 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(a or b) as being anticipated by Marra et al, Genbank Sequence Database (Accession No: AA073833), National Center for Biotechnology Information, National Library of Medicine, Bethesda, Maryland, publicly available on 1996.

Claim 1 is drawn to a naturally occurring sequence having 90% sequence identity with of SEQ ID NO:1, or an amino acid sequence of SEQ ID NO:1, or a biologically active fragment, or an antigencally active fragment of SEQ ID NO:1.

Marra et al teach a DNA sequence, the encoded amino acid sequence of which is 94% similar to SEQ ID NO:1, from amino acid 86 to 240, under MPSRCH sequence similarity search (us-09-170-980b-1.rst, pp.2-3).

Given the DNA sequence taught by Marra et al, one of ordinary skill in the art would immediately envision the claimed sequence.

The reference does not specifically teach that the sequence is naturally occurring, or biologically active or antigenically active. However, the claimed therapeutic agents appears to be the same as the prior art therapeutic agents, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the

absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable diffrences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Moreover, a naturally occurring sequence reads on a product by process. The production of a product by a particular process does not impart novelty or unobviousnes to a product when the same product is taught by the prior art. This is particularly true when the properties of the product are not changed by the process in an unexpected manner. See In re Thorpe, 227 USPQ 964 (CAFC 1985); In re Marosi, 218 USPQ 289, 292-293 (CAFC 1983); In re Brown, 173 USPQ 685 (CCPA 1972). Therefore, even if a particular process used to prepare a product is novel and unobvious over the prior art, the product per se, even when limited to the particular process, is unpatentable over the same product taught by the prior art. See In re Kind, 207 F.2d 618, 620, 43 USPQ 400, 402 (CCPA 1939); In re Merz, 97 F.2d 599, 601, 38 USPQ 143, 144-145 (CCPA 1938); In re Bergy, 563 F.2d 1031, 1035, 195 USPQ 344, 348 (CCPA 1977) *vacated* 438 U.S. 902 (1978); and United States v. Ciba-Geigy Corp., 508 F. Supp. 1157, 1171, 211 USPQ 529, 543 (DNJ 1979).

REJECTION UNDER 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 1, 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marra et al, *supra*, in view of Johnstone and Thorpe (Immunochemistry in Practice, 2nd Ed., 1987, Blackwell Scientific Publications, Oxford, pages 49-50).

Claims 1, 20 are drawn to a pharmaceutical composition comprising the following sequence in conjunction with a pharmaceutical carrier: a naturally occurring sequence having 90% sequence identity with of SEQ ID NO:1, or a biologically active fragment, or an antigencally active fragment of SEQ ID NO:1.

Claim 20 recites the claimed sequences, formulated as a pharmaceutical composition. However, this limitation is viewed as a recitation of intended use and therefore is not given patentable weight in comparing the claims with the prior art. Claim 20 read on the ingredient per se, which is a naturally occurring sequence having 90% sequence identity with of SEQ ID NO:1, or a biologically active fragment, or an antigencally active fragment of SEQ ID NO:1, in conjunction with a pharmaceutical carrier.

The teaching of Marra et al has been set forth.

Marra et al however do not teach a composition in a pharmaceutical carrier.

Johnstone and Thorpe teach that it was common practice in the art at the time of applicant's invention to formulate compositions of antibodies and PBS, which is considered to be an acceptable carrier for storage of antibodies, p. 49 and 50.

It is well known in the art that antibodies are polypeptides.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include a carrier in the composition because Johnstone and Thorpe teach that it was common practice in the art at the time of applicant's invention to formulate compositions of antibodies and PBS, which is considered to be an acceptable carrier for storage of antibodies, p. 49 and 50, and because it is well known in the art that antibodies are polypeptides. One of ordinary skill would have been motivated to do so in order to develop compositions suitable for storage. Finally, it has been held by the Court that a compound and a carrier are obvious, if it is obvious in the art to utilize a carrier with related compounds. See *In re Rosicky*, 125 USPQ 341 (CCPA 1960).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Tam B. Davis whose telephone number is (703) 305-2008. The examiner can normally be reached on Monday-Friday from 9:30am to 3:30pm, except on Wesnesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4227.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0916.

Minh-Tam B. Davis

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

December 20, 2000